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EXAMINER	
HILL, KEVIN KAI	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,657	DING ET AL.	
	Examiner	Art Unit	
	Kevin K. Hill, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. Applicant's response to the Requirement for Restriction, filed on July 26, 2007 is acknowledged.

Applicant has elected the invention of Group I, Claims 38-53, drawn to a vitellogenin expression vector and a transgenic eukaryotic host cell comprising said expression vector.

2. Election of Applicant's invention(s) was made without traverse. Because Applicant did not distinctly and specifically point out the supposed errors in the Group or species restriction requirement, the election has been treated as an election without traverse and the restriction and election requirement is deemed proper and therefore made final (MPEP § 818).

Amendments

3. In the reply filed July 26, 2007, Applicant has cancelled Claims 1-37 and 54-74. Claims 38-53 are under consideration.

Priority

4. This application is a 371 of PCT/SG03/00266, filed November 1, 2003 which claims benefit of the parent provisional application 60/425,263, filed November 12, 2002. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

Applicant has filed an Information Disclosure Statements on July 5, 2005 that has been considered. The signed and initialed PTO Form 1449 is mailed with this action.

Claim Objections

5. **Claims 38 and 44 are objected to because of the following informalities:**

With respect to claim 38, the word "comripsing" appears to be a typographical error for the word "comprising".

With respect to claim 44, the claim does not necessarily require the transgenic eukaryotic host to comprise the same expression vector as the feed or feed additive. The Examiner respectfully suggests placing the phrase "comprising the expression vector according to claim 38" immediately after "eukaryotic host" to improve clarity and precision of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. **Claim 44 is rejected under 35 U.S.C. 101** because the claimed invention is directed to non-statutory subject matter.

The claims are directed to "transgenic eukaryotic hosts" transduced with the claimed expression vector comprising a vitellogenin gene operably linked to a promoter, without restriction as to the eukaryotic host organism. The art recognizes that humans are eukaryotic organisms. Humans, transgenic or otherwise, are non-statutory subject matter.

This rejection would be overcome by limiting the eukaryotic hosts to "non-human eukaryotic hosts".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. **Claims 38-53 are rejected under 35 U.S.C. 112, first paragraph**, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claimed invention is directed to an expression vector comprising a vitellogenin gene operably linked to a promoter. At issue for the purpose of written description requirements is the lack of written support in the specification for the genus of vitellogenin genes. When the claims are analyzed in light of the specification, instant invention recites/encompasses the nucleic acids SEQ ID NOs: 1-20 encoding vitellogenin.

> *Vas-cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not clearly allow persons of ordinary skill in the art to recognize that (he or she) invented what is claimed." (See *Vas-cath* at page 1116). _

The disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. (see *In re Shokal* 113USPQ283(CCPA1957); *Purdue Pharma L.P. vs Faulding Inc.* 56 USPQ2nd 1481 (CAFC 2000).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, SEQ ID NOs: 1-20 are the only nucleic acid species encoding vitellogenin whose complete structure is disclosed.

Next, then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other identifying characteristic is that the vitellogenin gene would encode a polypeptide functionally equivalent to a reference vitellogenin

polypeptide, wherein one or more amino acid deletions, substitutions, modifications or additions may be present. While the specification discloses that the genus of vitellogenin structural variants should retain normal biological function, the specification does not disclose the normal biological function for each of the vitellogenins identified in the art at the time of the invention (pg 7, [0032]). The art recognizes that the vitellogenin gene family comprises vitellogenin, DSC-4 (defecation suppressor of *clk-1*), APOB, (apolipoprotein B), apolipophorin I, apolipophorin II, and MTP/Mttp (microsomal triglyceride transfer protein), wherein family members share a common amino-terminal "vitellogenin domain" (Brandt et al, BioEssays 27:339-346, 2005; pg 343, Box 2). However, the known vitellogenins are not functionally equivalent and the breadth of their respective "biological functions" are not fully known. The specification does not teach any modification to a nucleic acid encoding a vitellogenin polypeptide so as to provide the necessary guidance to the artisan as to what changes may be made in the polypeptide while retaining normal biological function to the vitellogenin genus.

A claimed cDNA nucleic acid (SEQ ID NO:1) does not read on a genomic sequence because full-length cDNAs would not be expected to contain introns or transcriptional regulatory elements such as promoters and enhancers that are found in genomic DNA. The art indicates that the structure of genes with naturally occurring regulatory elements and untranslated regions is empirically determined. For example, the structural elements of "gene" mediating the expression of a particular protein in the liver may be different than the structural elements of the "gene" mediating the expression of the same protein in the brain. Therefore, the structure of these elements which Applicant considers as being essential to the function of the claim are not conventional in the art. There is no known or disclosed correlation between the function of the gene product, vitellogenin, and the structure of the non-described regulatory elements and untranslated regions of the vitellogenin gene. Furthermore, there is no additional disclosure of physical and/or chemical properties. It is noted that all these vitellogenin genes vary greatly in structure and function and therefore each represents a subgenus. Again, the members of any of the subgenuses themselves would have very different structure and the specification does not provide any description of any identifying characteristics of the species of the subgenuses.

The Revised Interim Guidelines state:

"The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art" (col. 3, page 71434), "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (col. 2, page 71436).

An Applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

Possession may also be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention. See, e.g., *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 1 19 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998), *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997)*, *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. See *Fiers v. Revel*, 25 USPQ2d 1602 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. *In Fiddes*, claims directed to mammalian FGF's were found to be

unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Without a correlation between structure and function, the claim does little more than define the claimed invention by function. That is not sufficient to satisfy the written description requirement. *See Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is").

The Applicant has not provided any description or reduction to practice of nucleic acids encoding a vitellogenin polypeptide besides SEQ ID NOs: 1-20. Based on the Applicant's specification, the skilled artisan cannot envision the detailed chemical structure of the nucleotide sequences of vitellogenin genes as defined by the specification and encompassed by the claims. The few species of nucleic acids specifically disclosed are not representative of the genus because the genus is highly variant.

Accordingly, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that the Applicant is in possession of the broad genus of vitellogenin genes, besides those nucleic acids SEQ ID NOs:1-20 encoding vitellogenin polypeptides, at the time the application was filed.

Thus, for the reasons outlined above, it is concluded that the claims do not meet the requirements for written description under 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

8. **Claims 38-53 are rejected under 35 U.S.C. 112, first paragraph**, because the specification, while being enabling for a transgenic yeast comprising an expression vector, wherein said expression vector comprises a vitellogenin gene operably linked to a promoter functional in yeast, does not reasonably provide enablement for an enormous genus of transgenic eukaryotic host organisms. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention. If not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (*In re Wands*, 858 F.2d 731, 737, 8 USPQ2ds 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification. Therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention. And thus, skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The Breadth of the Claims and The Nature of the Invention

With respect to the expression vector comprising a vitellogenin gene, the claims are broad for encompassing an enormous genus of structurally distinct and non-obvious variations of nucleic acids encoding a genus of vitellogenin family members. The claims are also broad for encompassing an enormous genus of regulatory elements that promote the constitutive expression of said enormous genus of transgenes.

With respect to the transgenic eukaryotes, the claims are broad for encompassing an enormous genus of transgenic vertebrate, invertebrate, animal, plant and single-celled eukaryotic host organisms.

When the claims are analyzed in light of the specification, the nature of the invention is transgenic yeast, specifically *Pichia pastoris*, comprising an expression vector in which the GAPDH promoter is operably linked to the vitellogenin gene of SEQ ID NO:1.

The Existence of Working Examples and The Amount of Direction Provided by the Inventor

The specification does not define the term "vitellogenin". Rather, the specification discloses the term to embrace those genes known in the public databases, as well as a "functional equivalent" that differs from a reference vitellogenin polypeptide by one or more amino acid deletions, substitutions, modifications or additions that do not affect the normal biological function of vitellogenin (pg 7, [0032]). However, the specification does not teach the normal biological function of the genus of vitellogenin family members extant in the enormous genus of eukaryotic organisms, including those vitellogenins not yet known in the art, nor does the specification disclose which portions of the enormous genus of vitellogenin polypeptides in the eukaryotic kingdom may be altered by one or more amino acid deletions, substitutions, modifications or additions so as to retain the normal biological function, whatever that may be, respectively.

Furthermore, the claims recite the term "gene" that reasonably embraces nucleic acids encoding both protein-coding (exons) and protein non-coding (intron) sequences. While SEQ ID NO:1 is a complementary DNA (cDNA) sequence in which the non-coding introns have been removed, the specification does not teach how to use the inventive "vitellogenin gene" in the enormous genus of eukaryotic host organisms so that the intron sequences will be properly spliced out of the primary RNA transcript, thereby allowing translation and expression of the vitellogenin polypeptide.

The specification discloses the transgenic eukaryotic cell is a yeast cell, e.g. *S. cerevisiae* or *P. pastoris* (pg 11, [0046]), and expression plasmids encoding SEQ ID NO:1 (pg 14, [0059]-pg 16, [0063]), wherein *P. pastoris* was transfected with said plasmids encoding SEQ ID NO:1.

The specification does not teach means of genetically transforming the genus of eukaryotic host organisms embraced by the claims. While Applicant contemplates the transgenic eukaryote to be used as a feed or feed additive, the specification is silent regarding the ability to create transgenic eukaryotic animals and plants representative of the full scope of the claims, e.g. squid, taro or portabellos, for example.

The State of the Prior Art, The Level of One of Ordinary Skill and The Level of Predictability in the Art

With respect to the genus of vitellogenin genes, the art recognizes that the vitellogenin gene family comprises vitollogenin, DSC-4 (defecation suppressor of *clk-1*), APOB, (apolipoprotein B), apolipophorin I, apolipophorin II, and MTP/Mttp (microsomal triglyceride transfer protein), wherein family members share a common amino-terminal "vitellogenin domain" (Brandt et al, BioEssays 27:339-346, 2005; pg 343, Box 2).

With respect to the enormous genus of transgenic eukaryotic host organisms, the art is silent with respect to the predictable transformation and heterologous expression of an artisan's desired gene of interest. Simple heterologous expression constructs in yeast host systems are clearly structurally different from heterologous expression constructs in other host systems, including plants and animals. Required are different promoters, enhancer, codon optimization, termination regions, and other regulatory regions. It is unclear what regions of Applicant's yeast expression vector should be retained, and what regions should be modified, to obtain an expression vector that would be operable in an animal or plant cell. The art is silent, for example, regarding the ability to create transgenic squid, taro plants or portabello mushrooms, each recognized in the art as food sources.

With respect to the method(s) of making a transgenic non-human animal, the art recognizes that ES cells have yet to be identified in animal species other than mouse. For example, Kuroiwa et al (Nature Genetics 36(7):775-80, 2004; Epub 2004 June 6) teach the ES cells suitable for gene targeting are not available for species other than mouse. Moreadith et al (J. Mol. Med. 75(3): 208-216, 1997; p. 214, Summary) note that "putative" ES cells found in other animals beyond mouse lack a demonstration of the cell to give rise to germline tissue (germline transmission) or the whole animal (totipotency), a demonstration for an art-recognized property of ES cells.

More specifically as to the lack of reasonable correlation between rodent and other species in ES technology, Polejaeva et al. (Theriogenology, 53(1):117-126, 2000), states:

> "Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The

most profound is that DNA can only be added, not deleted, or modified *in situ*. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro- nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could require the generation of several transgenic founder lines" (see page 119).

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system at present and that only "putative" ES cells exist for other species. See Rulicke et al (Experimental Physiology 85: 589-601, 2000; pg 589, col. 2, last ¶), who supports this observation, wherein Rulicke et al disclose:

"The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far."

While methods to generate transgenic mice in whose genome a transgene may integrate are known in the art, the specification fails to teach methods of generating any other transgenic animals or other murine species. The murine subgenus encompasses more than 1383 species of rodents, whose ES cells were yet to be discovered at the time of instant priority date and as of today, and the state of the art supports that only ES cells from laboratory mouse strains were available for use for production of transgenic mice.

Concerning the position of genome insertion of a polynucleotide encoding a vitellogenin gene belonging to the large genus of vitellogenin protein family, it is important because the position may influence the phenotype of the transgenic eukaryote. The phenotype of the transgenic eukaryote is a necessary element that the specification must teach to enable one skilled in the art concerning how to use the transgenic eukaryote for its disclosed utility when considering the enablement of the invention. Without any phenotype, one skilled in the art would

not know how to use the claimed transgenic eukaryote even though its genome comprises a vitellogenin gene belonging to the large genus of vitellogenin protein family operably linked to a constitutive promoter.

One of skill would not be able to rely on the state of the transgenic art or the teaching of the specification to predictably produce transgenic eukaryotes for the breadth claimed. This is because the transgenic art has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome, which would vary among different species of eukaryotes. The elements of the particular construct used to make transgenic animals are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene; e.g., specific promoters, presence or absence of introns, etc (Houdebine, J. Biotech. 34: 269-287, 1994; pg 281).

The specification teaches only how to use transgenic yeast, specifically *Pichia pastoris*, having the desired transgene-dependent phenotypic alteration. The mere capability to perform gene transfer in a given species is not enabling for the claimed genus of transgenic eukaryotes because the desired phenotypes cannot be predictably achieved simply because the animal has the desired genotype. This is because the art of transgenic animals has for many years stated that the unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have within their cells cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the genome (Kappel et al, Current Opinion in Biotechnology 3: 548-553, 1992; pg 549, col. 2, ¶ 2). "The position effect" and unidentified control elements also are recognized to cause aberrant expression (Wall, Theriogenology 45: 57-68, 1996; pg 61, ¶2, line 9 to pg 62, line 3). Well-regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues. Additional factors influencing low expression, or the lack their of, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct. These factors, thus, are copy number independent and integration site dependent, emphasizing the role the integration site plays on expression of the transgene (Cameron, Molec. Biotech. 7: 253-265, 1997; pg 256, lines 3-13, col. 1-2, joining ¶).

Since the Applicants have not disclosed other eukaryotic species encompassed by the claims, it is highly unpredictable of the outcome of the recited method in making any transgenic eukaryote. Taken together, the current status of transgenic art is such that generating transgenic eukaryotes with a requisite phenotype is neither routine nor predictable, unless proven by a working example, let alone a claim that embraces the enormous genus of eukaryotic plants, animals, vertebrates and invertebrates, and fungi known in the world. The level of one of ordinary skill in the transgenic art is considered to be high. It is not apparent as to how one skilled in the art reasonably correlates, without undue experimentation, between the *Pichia pastoris* yeast expressing a heterologous protein and any transgenic non-human mammal or plant, or non-yeast fungus, particularly in view of the foregoing reasons.

The Quantity of Any Necessary Experimentation to Make or Use the Invention

To require one skilled in the art to randomly make changes to Applicant's yeast expression vector, or to generate their own expression vector without guidance as to how inoperable embodiments can be readily eliminated other than by trial and error, is an invitation to experiment, requiring excessive and undue experimentation. Accordingly, Applicant has not enabled an expression vector encoding a genus of vitellogenin genes commensurate in scope to the enormous genus of eukaryotic host organisms encompassed by the claims.

The instant portion of the invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech Inc v. Novo NordiskA/S* 42 USPQ2d 1001, at 1005). The claimed genus of transgenic eukaryotic hosts constitutes such a "germ of an idea".

The courts have stated that reasonable correlation must exist between scope of exclusive right to patent application and scope of enablement set forth in patent application. 27 USPQ2d 1662 *Exparte Maizel.* In the instant case, in view of the lack of guidance, working examples,

breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed in the enormous genus of vertebrate, invertebrate, animal, plant or single-celled eukaryotic organisms.

In conclusion, the specification fails to provide any guidance as to how an artisan would have dealt with the art-recognized limitations of the claimed method commensurate with the scope of the claimed invention and therefore, limiting the claimed invention to a transgenic yeast comprising an expression vector, wherein said expression vector comprises a vitellogenin gene operably linked to a promoter functional in yeast, is proper.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the Applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the Applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the Applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. **Claims 38 and 44 are rejected under 35 U.S.C. 102(b)** as being anticipated by Yan et al (Developmental Biology 140: 281-290, 1990; *of record in IDS).

Yan et al teach transgenic flies comprising an expression vector comprising a vitellogenin gene operably linked to a promoter, wherein the promoter is functional in a eukaryotic host, specifically a fly.

Yan et al do not teach the fly is suitable for use as a feed or feed additive; however, the art recognizes that flies are a food source for fish, birds, reptiles, amphibians, and insects, for

example (http://www.buyfruitflies.com/fruitfly_info.html, last visited September 10, 2007). To the extent that the claim does not recite the intended organism to consume the feed/feed additive, nor the degree of "suitable", absent evidence to the contrary, the transgenic flies of Yan et al fulfill the instant claims.

10. **Claims 38 and 44 are rejected under 35 U.S.C. 102(b)** as being anticipated by Grant et al (Mol. Biol. Cell 10: 4311-4326, 1999).

Grant et al teach transgenic worms comprising an expression vector comprising a vitellogenin gene operably linked to a promoter, wherein the promoter is functional in a eukaryotic host, specifically a worm.

Grant et al do not teach the worms as being suitable for use as a feed or feed additive; however, the art recognizes that worms are a food source for pseudoscorpions as well as fungus (http://www.css.cornell.edu/compost/invertebrates.html, http://www.virtualmuseum.ca/~mushroom/English/Science/Lifestyles/predators.html, last visited September 10, 2007). To the extent that the claim does not recite the intended organism to consume the feed/feed additive, nor the degree of "suitable", absent evidence to the contrary, the transgenic worms of Grant et al fulfill the instant claims.

11. **Claims 38-39 and 44-45 are rejected under 35 U.S.C. 102(b)** as being anticipated by Bradbury et al (J. Biol. Chem. 274(5):3159-3164, 1999).

Bradbury et al teach the generation of transgenic yeast comprising an expression vector comprising a vitellogenin gene, specifically microsomal triglyceride transfer protein (MTP), wherein the nucleic acid comprising said MTP gene is operably linked to a promoter that is functional in yeast.

Bradbury et al do not teach the transgenic yeast as intended feed/feed additive; however, the intended use is not given patentable weight because the art recognizes that yeast may be used as a food/food additive and the transgenic yeast of Bradbury et al fulfill the structural limitations of the instant claims.

12. **Claims 38-39 and 44-46 are rejected under 35 U.S.C. 102(b)** as being anticipated by Nusbaum et al (Nature Genetics 22: 388-393, 1999).

Nusbaum et al teach the generation of transgenic yeast comprising yeast artificial chromosomes comprising segments of the mouse genome.

Nusbaum et al do not teach the expression of the genes, nor the explicit cloning of at least one murine vitellogenin gene. However, absent evidence to the contrary, one of ordinary skill in the art would reasonably expect and/or conclude that at least one YAC clone comprises at least one murine vitellogenin gene because Nusbaum et al teach the YAC library to cover approximately 92% of the mouse genome. To the extent that the claims recite the promoter is functional in a yeast, the claims do not recite the degree of expression. Absent evidence to the contrary, at least some RNA transcripts are synthesized from the murine vitellogenin gene encoded by the YAC clone.

13. **Claims 38-40 and 44-46 are rejected under 35 U.S.C. 102(a) and 102(e)** as being anticipated by Jacobs et al (U.S. 2001/0039335 A1).

Jacobs et al disclose a polynucleotide encoding a polypeptide having similarity to a chicken vitellogenin (pg 127, [3373], col. 2, lines 17-20), wherein said polynucleotide may be expressed heterologously in yeast cells such as *Saccharomyces cerevisiae* or *Schizosaccharomyces pombe* (pg 165, [3844]), wherein the expression vector may be integrated into the host cell genome (pg 163, [3832]), wherein said polypeptide encoded by said polynucleotide may be expressed constitutively or tissue-specifically (pg 166, [3856]), wherein one of ordinary skill in the art would understand that constitutive or tissue-specific expression inherently requires the use of constitutive or tissue-specific promoter, respectively.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the Examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the Examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. **Claims 38-41 and 44-53 are rejected under 35 U.S.C. 103(a)** as being unpatentable over Cregg et al (Molecular Biotechnology 16: 23-52, 2000) and Bradbury et al (J. Biol. Chem. 274(5):3159-3164, 1999).

Cregg et al teach that, at the time of publication, more than 200 different heterologous proteins expressed in the yeast *P. pastoris* had been published (pg 23, col. 2, Figure 1, Table 3), and a website has been created and maintained that lists such heterologous proteins. *P. pastoris* is a eukaryote capable of many of the post-translational modifications performed by higher eukaryotic cells, and is generally regarded as being faster, easier and less expensive to use than expression systems derived from higher eukaryotes, and usually gives higher expression levels (pg 24, col. 1). *P. pastoris* has long been used for the generation of yeast biomass or single-cell protein to be marketed primarily as high-protein animal feed (pg 24, col. 2, ¶1). Protease-deficient strains are available (pg 26, Table 1), as well as expression vectors for intracellular or secretion of the heterologous protein (pg 27, Table 2), wherein said vectors comprise dominant drug-resistance markers that allow for enrichment of strains that receive multiple copies of foreign gene expression cassettes, wherein said vectors may integrate into the yeast host genome (pg 28, col. 1, ¶2; pg 29, col. 1). Cregg et al teach that the yeast GAP promoter is a strong constitutive promoter (pg 28, col. 2, ¶2).

Cregg et al do not teach the yeast expressing a vitellogenin gene; however, at the time of the invention, Bradbury et al taught the generation of transgenic yeast comprising an expression

vector comprising a vitellogenin gene, specifically microsomal triglyceride transfer protein (MTP), wherein the nucleic acid comprising said MTP gene is operably linked to a promoter that is functional in yeast.

Neither Cregg et al nor Bradbury et al teach that the amino acid contents, lipid contents and level of polyunsaturated fatty acids are increased in the transgenic yeasts expressing vitellogenin. However, absent evidence to the contrary, the recited increases in the recited subject matter is considered to be inherent features of the invention because the specification discloses that a host cell expressing vitellogenin inherently possesses increased levels of amino acids and lipids such as poly-unsaturated fatty acids as a consequence of expressing vitellogenin (pg 37, [00127]).

Neither Cregg et al nor Bradbury et al teach the vitellogenin nucleic acid of SEQ ID NO:1. However, absent evidence to the contrary, nothing non-obvious is seen with expressing a vitellogenin gene of SEQ ID NO:1 in yeast because the art has long-recognized the ability to express heterologous polypeptides such as vitellogenin in yeast. The substitution of one known element for another known element would have yielded predictable results to one of ordinary skill in the art at the time of the invention.

Thus, the invention as a whole is *prima facie* obvious.

Conclusion

15. No claims are allowed. The expression vectors recited in claims 42-43 comprising the nucleic acid cDNA of SEQ ID NO:1 encoding a vitellogenin polypeptide are free of the prior art.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The Examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Joseph T. Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER